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THE STRUCTURE OF MACELIGNAN FROM *MYRISTICA FRAGRANS**

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Key Word Index—*Myristica fragrans*; Myristicaceae; lignans; macelignan.

Abstract—A new lignan, macelignan, isolated from the arils of *Myristica fragrans*, is shown to have the structure (2*R*,3*S*)-1-(3,4-methylenedioxyphenyl)-2,3-dimethyl-4-(4-hydroxy-3-methoxyphenyl)-butane by spectral analysis, chemical conversion and X-ray crystallographic analysis.

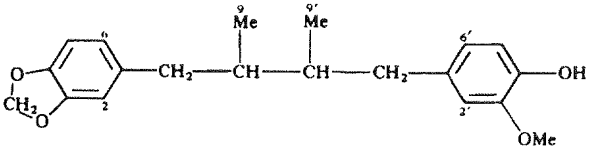
An ether extract of the arils of *Myristica fragrans* Houtt. caused a significant alteration in hepatic enzyme activities [1]. Systematic fractionation by silica gel column chromatography of the extract monitored by an animal test gave a new lignan tentatively named macelignan (1), as an active principle, together with a biologically inactive known compound, *meso*-dihydroguaiaretic acid. The structure of macelignan, $C_{20}H_{24}O_4$, was suggested to be a 2,3-dimethyl-1,4-diaryl-butane type lignan with a 4-hydroxy-3-methoxybenzyl unit and a 3,4-methylenedioxybenzyl unit from the IR, MS and NMR spectra of the compound and its acetate (see Experimental), together with negative responses of the compound in Gibbs and Emerson tests. Selective cleavage of the methylenedioxy group of 1 with boron trichloride, followed by methylation gave dimethyl *meso*-dihydroguaiaretic acid. Hence two methyl groups in this lignan are found to be in *cis* orientation.

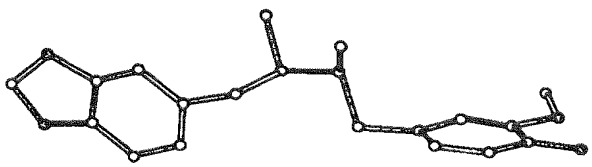
For a complete stereochemical study 1 was subjected to X-ray crystallographic analysis, from which its structure was established as (2*R*,3*S*)-1-(3,4-methylenedioxyphenyl)-2,3-dimethyl-4-(4-hydroxy-3-methoxyphenyl)-butane. Macelignan is a diastereoisomer of austrobailignan-6, which was isolated previously from *Austrobaileya scandens* [2].

EXPERIMENTAL

Isolation of lignans. Dried mace (590 g) was coarsely powdered and extracted × 4 with Et_2O. The Et_2O extract on removal of solvent gave a reddish brown viscous solid (260 g). The non-volatile residue (20 g) after removal of volatile essential oils by steam distillation was chromatographed on a silica gel column by gradient elution with mixtures of C_6H_6 and Et_2O (1:0–2:1) to give 7 fractions.

From fraction 1, macelignan (1) was obtained as a pale yellow oil which on recrystallization from *n*-hexane–Et_2O (1:1) gave colourless prisms (1.5 g), mp 70–72°, $[\alpha]_D^{20} = +5.28°$ (*c* = 1.8, $CHCl_3$), R_f 0.66 (C_6H_6–Et_2O = 4:1), $FeCl_3$ in EtOH, green. UV λ_{max}^{MeOH} nm (log ε): 213 (3.97), 230 (3.88) and 285 (3.77); IR ν_{max}^{KBr} cm^{-1}: 3480 (OH), 1852, 1740, 1610, 1514, 1500, 1486, 1440 (aromatic), 1376, 1250, 1028 and 926 (O-CH_2-O); MS *m/z* (rel. int.): 328 $[M]^+$ (11), 137 $[C_8H_9O_2]^+$ (100) and 135 $[C_8H_7O_2]^+$ (68); ^1H NMR ($CDCl_3$ at 360 MHz): δ 6.82 (1H, *d*, *J* = 7.9)/6.72 (1H, *d*, *J* = 7.8) (H-5/5'), 6.65 (1H, *d*, *J* = 1.8), 6.61 (1H, *d*, *J* = 1.6) (H-2/2'), 6.64 (1H, *dd*, *J* = 1.8 and 7.9), 6.6 (1H, *dd*, *J* = 1.6 and 7.8) (H-6/6'), 5.913 (1H, *d*, *J* = 2.1), 5.909 (1H, *d*, *J* = 2.1) (O–CH_2–O), 5.48 (1H, *s*, 4'–OH), 3.86 (3H, *s*, –OCH_3), 2.72 (2H, *dd*, *J* = 4.9 and 13.7, H-7a and -7'a), 2.28 (1H, *dd*, *J* = 9.2 and 13.7), 2.25 (1H, *dd*, *J* = 9.4 and 13.7) (H-7b/7'b), 1.77–1.67 (2H, *m*, H-8 and -8') and 0.83 (3H, *d*, *J* = 6.6), 0.82 (3H, *d*, *J* = 6.6) (H-9/9'); ^{13}C NMR ($CDCl_3$ at 20 Mz): 147.7 (C-3), 146.6 (C-3'), 145.6 (C-4), 143.8 (C-4'), 135.7 (C-1), 133.8 (C-1'), 121.8 (C-6 and -6'), 114.2 (C-5'), 111.7 (C-2'), 109.4 (C-5), 108 (C-2), 100.7





○ C
● O

Configuration of macelignan by X-ray crystallography.

*Part 9 in the series "Studies on crude drugs acting on drug-metabolizing enzymes". For part 8 see ref. [1].

(O–CH_2–O), 55.9 (–OCH_3), 39.5/39.4 (C-8/8'), 39.2/39.0 (C-7/7') and 16.3/16.2 (C-9/9').

Fraction 3 (3.4 g) on crystallization gave *meso*-dihydroguaiaretic acid as colourless prisms (56 mg), mp 82–84° (lit. 88–89.5° [3]), $[\alpha]_D^{20} = 0°$ ($c = 1.0$, $CHCl_3$), R_f 0.36, which was identical by mmp, UV, IR and ^{1}H NMR with an authentic sample.

X-Ray structure analysis of macelignan (1). Crystal data; $a = 6.652$ Å, $b = 11.091$ Å, $c = 13.121$ Å; $\alpha = 69.18°$, $\beta = \gamma = 90°$; space group $P2_1$ (unique *a*); $Z = 2$, $D_{meas} = 1.22\,gcm^{-3}$, $D_{calc} = 1.25\,gcm^{-3}$. On a Nicolet R3m diffractometer 1398 unique reflections were measured up to $2\,\vartheta = 114°$ with Ni-filtered CuK_α-radiations [1316 observed with $I \geq 3\sigma(I)$]. The structure was solved with direct methods using SHELXTL*. The first approach showed all nonhydrogen atoms in the E-map as drawn in the structures. The hydrogen positions were calculated from the carbon that they are bound to (except the one in the hydroxyl group). The atomic coordinates are deposited at the Cambridge Crystallographic Data Centre. The refinement of the structure yielded an *R* factor of 8.4%.

Acetylation of macelignan (1). A soln of 1 (30 mg) in a mixture of pyridine (0.5 ml) and Ac_2O (0.5 ml) was allowed to stand at room temp. overnight, then diluted with H_2O and extracted with Et_2O. The Et_2O soln was washed with 5% $NaHCO_3$, then H_2O, dried over Na_2SO_4 and concentrated. The residue was chromatographed (solvent: $CHCl_3$) to give an acetate as a colourless glassy material which could not be crystallized. This compound did not absorb in the region corresponding to an OH group.

^{1}H NMR ($CDCl_3$ at 80 MHz): 6.87–6.53 (6H, *m*, H-2,2', 5,5', 6 and 6'), 5.91 (2H, *s*, O–CH_2–O), 3.8 (3H, *s*, –OCH_3), 2.78 (1H, *dd*, $J = 4.2$ and 13.2), 2.72 (1H, *dd*, $J = 5.3$ and 13.2) (H-7a/7a'), 2.3 (1H, *dd*, $J = 8.8$ and 13.2), 2.27 (1H, *dd*, $J = 9.3$ and 13.2) (H-7b/7'b), 2.29 (3H, *s*, CH_3CO), 1.96–1.49 (2H, *m*, H-8 and -8') and 0.85 (6H, *d*, $J = 6.4$, H-9 and -9').

Cleavage of methylenedioxy group of macelignan followed by methylation. To a soln of 32.8 mg of 1 in 1.5 ml of CH_2Cl_2 at 4° was added 0.8 ml of a CH_2Cl_2 containing 23.4 mg of boron trichloride, stirred at room temp. for 6 hr, then 5 ml of MeOH added and evaporated to dryness. $(CH_3)_2SO_4$ (0.2 ml) and K_2CO_3 (0.6 g) were added to a soln of the reaction product in dry Me_2CO and mixture stirred at 40° for 5 hr, then diluted with H_2O and extracted with Et_2O. After washing, drying and conc. The residue was recrystallized from *n*-hexane–Et_2O (1:1) to give *meso*-dihydroguaiaretic acid dimethylether as colourless needles (20 mg), mp 96–98° (lit. 99–101° [4]), $[\alpha]_D^{20} = 0°$ ($c = 0.8$, $CHCl_3$), which was identical by mmp, ^{1}H NMR with an authentic sample.

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*G. M. Sheldrick, SHELXTL (Release 4.1), A Program for Crystal Structure Determination, Cambridge–Göttingen 1983.

REFERENCES

1. Shin, K. H. and Woo, W. S. (1986) *Kor. J. Pharmacogn.* **17**, 189.
2. Murphy, S. T., Ritchie, E. and Taylor, W. S. (1975) *Aust. J. Chem.* **28**, 81.
3. Ikeya, Y., Taguchi, H., Yosioka, I. and Kobayashi, H. (1979) *Chem. Pharm. Bull.* **27**, 1583.
4. Liu, J.-S., Hung, M.-F., Gao, Y.-L. and Findlay, J. A. (1981) *Can. J. Chem.* **59**, 1680.